Please add the following new claims:

--7. The method of claim 6, wherein the agent is selected irrespective of its ability to inhibit FKBP-12 rotamase activity.

8. The method of claim 6, wherein selecting a FK506 analog that does not bind FKBP-12 comprises selecting a FK506 analog that binds to FKBP-12 with an apparent K_d of greater than 10 μM.

9. The method of claim 6, wherein selecting a FK506 analog that does not bind FKBP-12 comprises selecting a FK506 analog that binds to FKBP-12 with an apparent K_d of greater than 30 μM.

10. The method of claim 6, wherein selecting a FK506 analog that does not bind FKBP-12 comprises selecting a FK506 analog that binds to FKBP-12 with an apparent K_d of greater than 100 μM.

11. The method of claim 6 wherein selecting a FK506 analog that does not bind FKBP-12 comprises selecting a FK506 analog that does not substantially inhibit FKBP-12 rotomase activity.

12. A method of identifying a non-binding FK506 analog that stimulates nerve cell growth, the method comprising:

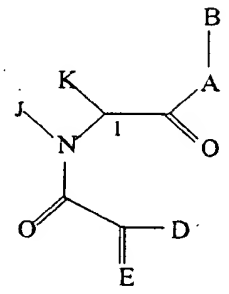
screening a plurality of FK506 analogs for binding to FKBP-12 and for rotamase inhibition activity;

selecting a FK506 analog of interest that does not bind FKBP-12 and which has low rotamase inhibition; and

assaying the FK506 analog of interest for activity in promoting cell growth.

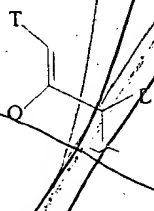
13. The method of claim 6, wherein the FK506 analog is selected from the groups consisting of compounds of the formula:

formula 1



wherein A is O,NH,or N-(C1-C4 alkyl);

wherein B is hydrogen, CHL-Ar, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl, (C5-C7)-cycloalkenyl or Ar substituted (C1-C6)-alkyl or (C2-C6)-alkenyl, or



wherein L and Q are independently hydrogen, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl;

wherein T is Ar or substituted cyclohexyl with substituents at positions 3 and 4 that are independently selected from the group consisting of hydrogen, hydroxyl, O-(C1-C4)-alkyl or O-(C2-C4)-alkenyl and carbonyl;

wherein Ar is selected from the group consisting of 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl and phenyl having one to three substituents that are independently selected from the group consisting of hydrogen, halo, hydroxyl, nitro, CF_3, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl, O-(C1-C4)-straight or branched alkyl or O-(C2-C4)-straight or branched alkenyl, O-benzyl, O-phenyl, amino and phenyl;

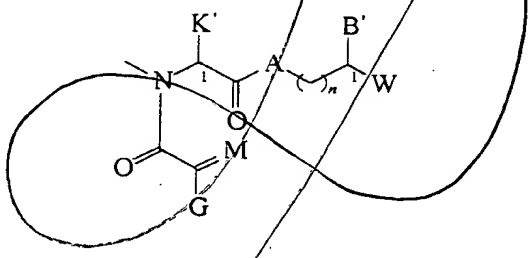
wherein D is U; E is either oxygen or CH-U, provided that if D is hydrogen, then E is CH-U or if E is oxygen, then D is not hydrogen;

wherein each U is independently selected from hydrogen, O-(C1-C4)-straight or branched alkyl or O-(C2-C4)-straight or branched alkenyl, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl or (C5-C7)-cycloalkenyl substituted with (C1-C4)-straight or branched alkyl or (C2-C4)-straight or branched alkenyl, 2-indolyl, 3-indolyl, [(C1-C4)-alkyl or (C2-C4)-alkenyl]-Ar or Ar;

wherein J is hydrogen or C1 or C2 alkyl or benzyl; K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylmethyl; or wherein J and K may be taken together to form a 5-7 membered heterocyclic ring that may contain an oxygen (O), sulfur (S), SO or SO_2 substituent therein; and the stereochemistry at position 1 is R or S;

compounds of the formula:

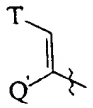
formula 2



wherein A' is CH_2, oxygen, NH, or N-(C1-C4 alkyl);

wherein B' and W are independently hydrogen, Ar', (C1-C10)-straight or branched alkyl, (C2-C10)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkenyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, or Ar' substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl wherein in each case, any one of the CH_2 groups of the alkyl, alkenyl, or alkynyl chains may be optionally replaced by a heteroatom selected from the group consisting of O, S, SO, SO_2, N, and NR, wherein R is selected from the group consisting of hydrogen, (C1-C4)-straight or branched alkyl, (C2-C4)-straight or branched alkenyl or alkynyl, and (C1-C4) bridging alkyl wherein a bridge is formed between the nitrogen and a carbon atom of the heteroatom-

containing chain to form a ring, and wherein the ring is optionally fused to an Ar' group, or



wherein Q' is hydrogen, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl or alkynyl;

wherein T' is Ar or substituted 5-7 membered cycloalkyl with substituents at positions 3 and 4 that are independently selected from the group consisting of oxo, hydrogen, hydroxyl, O-(C1-C4)-alkyl, and O-(C2-C4)-alkenyl;

wherein Ar' is a carboxcyclic aromatic group selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, and anthracenyl; or a heterocyclic aromatic group selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl;

wherein Ar' may contain one to three substituents that are independently selected from the group consisting of hydrogen, halogen, hydroxyl, hydroxymethyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl, O-[(C1-C4)-straight or branched alkyl], O-[(C2-C4)-straight or branched alkenyl], O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, carboxyl, N-[(C1-C5)-straight or branched alkyl or (C2-C5)-straight or branched alkenyl)carboxamides, N,N-di[(C1-C5)-straight or branched alkyl or (C2-C5)-straight or branched alkenyl]carboxamides, N-morpholinocarboxamide, N-benzylcarboxamide, N-thiomorpholinocarboxamide,

N-picolinoylcarboxamide, O-X, CH_2-$(CH_2)_q$-X, O-$(CH_2)_q$-X, $(CH_2)_q$-O-X,, and CH=CH-X;

wherein X is 4-methoxyphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazyl, quinolyl, 3,5-dimethylisoxazoyl, isoxazoyl, 2-methylthiazoyl, thiazoyl, 2-thienyl, 3-thienyl, or pyrimidyl; and q is 0-2;

wherein G is U';

wherein M is either oxygen or CH-U'; provided that if G is hydrogen, then M is CH-U' or if M is oxygen, then G is U';

wherein U' is hydrogen, O-[(C1-C4)-straight or branched alkyl] or O-[(C2-C4)-straight or branched alkenyl], (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl or (C5-C7)-cycloalkenyl substituted with (C1-C4)-straight or branched alkyl or (C2-C4)-straight or branched alkenyl, [(C1-C4)-alkyl or (C2-C4)-alkenyl]-Y or Y;

wherein Y is selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrolidinyl, 1,3-dioxolyl, 2-imidazolinyl, imidazolidinyl, 2H-pyranyl, 4H-pyranyl, piperidyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, quinuclidinyl, and heterocyclic aromatic groups as defined for Ar' above;

wherein Y may contain one to three substituents that are independently selected from the group consisting of hydrogen, halogen, hydroxyl, hydroxymethyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl, O-[(C1-C4)-straight or branched alkyl], O-[(C2-C4)-straight or branched alkenyl], O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, and carboxyl;

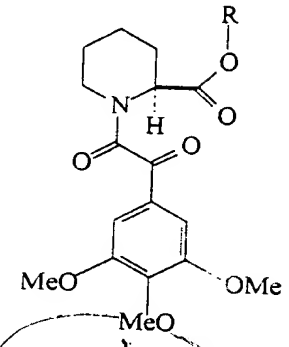
wherein J' is hydrogen, (C1-C2) alkyl or benzyl; wherein K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylmethyl, or wherein J' and K may be taken together to form a 5-7 membered heterocyclic ring that may contain a heteroatom selected from the group consisting of O, S, SO and SO_2;

wherein m is 0-3; and

wherein the stereochemistry at position 1 is R or S and the stereochemistry at position 2 is R or S;

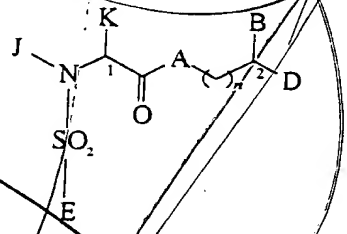
compounds of the formula:

formula 3



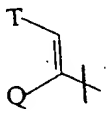
compounds of the formula:

formula 4



wherein A is CH_2, oxygen, NH or N-(C1-C4 alkyl);

wherein B and D are independently Ar, hydrogen, (C1-C6)-straight or branched alkyl, (C1-C6)-straight or branched alkenyl, (C1-C6)-straight or branched alkyl or alkenyl that is substituted with a (C5-C7)-cycloalkyl, (C1-C6)-straight or branched alkyl or alkenyl that is substituted with a (C5-C7)-cycloalkenyl, or Ar substituted (C1-C6)-straight or branched alkyl or alkenyl, wherein, in each case, one or two of the CH_2 groups of the alkyl or alkenyl chains may contain 1-2 heteroatoms selected from the group consisting of oxygen, sulfur, SO and SO_2 in chemically reasonable substitution patterns, or



provided that both B and D are not hydrogen;

wherein Q is hydrogen, (C1-C6)-straight or branched alkyl or (C1-C6)-straight or branched alkenyl;

wherein T is Ar or substituted 5-7 membered cycloalkyl with substituents at positions 3 and 4 that are independently selected from the group consisting of hydrogen, hydroxyl, O-(C1-C4)-alkyl, O-(C1-C4)-alkenyl and carbonyl;

wherein Ar is selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, monocyclic and bicyclic heterocyclic ring systems with individual ring sizes being 5 or 6 that may contain in either or both rings a total of 1-4 heteroatoms independently selected from O, N and S; wherein Ar may contain one to three substituents that are independently selected from the group consisting of hydrogen, halo, hydroxyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl, O-(C1-C4)-straight or branched alkyl, O-(C2-C4)-straight or branched alkenyl, O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, carboxyl and phenyl;

wherein E is (C1-C6)-straight or branched alkyl, (C1-C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl, (C5-C7)-cycloalkenyl substituted with (C1-C4)-straight or branched alkyl or (C1-C4)-straight or branched alkenyl, [(C2-C4)alkyl or (C2-C4)-alkenyl)]-Ar or Ar (Ar as described above);

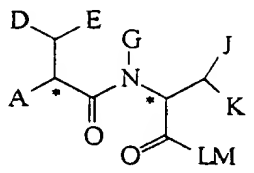
wherein J is hydrogen or C1 or C2 alkyl or benzyl; K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylmethyl; or wherein J and K may be taken together to form a 5-7 membered heterocyclic ring that may contain an oxygen, sulfur, S0 or SO_2 substituent therein; and;

wherein n is 0-3; and

wherein the stereochemistry at position 1 is R or S and the stereochemistry at position 2 being R or S;

compounds of the formula:

formula 5



wherein A is NH, O, S, or CH;

wherein if A is NH, O, or S, B is PCO- or POCO-, where P is a C1-C6 straight or branched alkyl or alkenyl group, a C5-C6 cycloalkyl or cycloalkenyl, or a methyl substituted with a C5-C6 cycloalkyl, C5-C6 cycloalkenyl, phenyl, 1-naphthyl, 2-naphthyl, 9-fluorenyl, or 1-adamantyl;

wherein if A is CH, then B is connected via a *trans* double bond and is a C2-C4 straight or branched alkyl or alkenyl group, or is a methyl or ethyl substituted with either a C5-C6 cyclic alkyl group or Ar, where Ar is selected from the group consisting of 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, phenyl and phenyl having one to three substituents that are independently selected from the group consisting of: hydroxyl, halo, nitro, CF_3, C1-C4 straight or branched alkyl or alkenyl, O-(C1-C4) straight or branched alkyl or alkenyl, and Ar, where Ar is selected from the group consisting of 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, phenyl and phenyl having one to three substituents that are independently selected from the group consisting of: hydroxyl, halo, nitro, CF_3, C1-C4 straight or branched alkyl or alkenyl, O-(C1-C4) straight or branched alkyl or alkenyl; wherein no more than two Ar groups may be linked together;

wherein D is hydrogen, C1-C4 straight or branched alkyl or alkenyl, hydroxy, tert-butyloxy, benzyloxy, 4-benzyloxyphenyl, cyclohexyl, $-(CH_2)_n-CO_2-Q$, where n=0 or 1 and Q is methyl, ethyl, i-propyl, t-butyl, benzyl, 1-naphthyl, 2-naphthyl, or cyclohexyl; or Ar, where Ar is selected from the group consisting of 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, phenyl and phenyl having one to three substituents that are independently selected from the group consisting of: hydroxyl, halo, nitro, CF_3, C1-C4 straight or branched alkyl or alkenyl, O-(C1-C4) straight or branched alkyl or alkenyl, and Ar, where Ar is selected from the group consisting of 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, phenyl and phenyl having one to three substituents that are independently selected from the group consisting of: hydroxyl, halo, nitro, CF_3, C1-C4 straight or branched alkyl or alkenyl, O-(C1-C4) straight or branched alkyl or alkenyl; wherein no more than two Ar groups may be linked together;

wherein E and K are independently hydrogen or methyl;

wherein G is either methyl or ethyl; J is hydrogen, C1-C6 straight or branched alkyl or alkenyl, C6-C6 cycloalkyl or cycloalkenyl, sulfhydryl, hydroxy, phenyl, 3-indolyl, or benzyl; wherein G and J may be connected by a bond to form a cycle of 5 or 6 members;

wherein L is O or an α-amino acid residue attached via the α-nitrogen, and selected from the group consisting of: alanine, 2-aminobutyric acid, valine, norvaline, leucine, norleucine, isoleucine, phenylalanine, cyclohexylalanine, tryptophan, 1-naphthylalanine, 2-naphthylalanine, threonine (side chain benzyl or tert-butyl ether), methionine, or serine (side chain benzyl or tert-butyl ether);

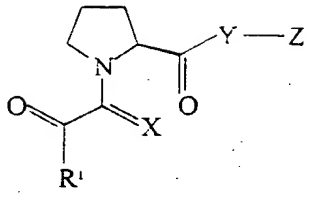
wherein if L is O, then M is C1-C6 straight or branched alkyl or alkenyl, or -$(CH_2)_n$-Ar, where n=1-6 and Ar is selected from the group consisting of: 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, phenyl and phenyl having one to three substituents that are independently selected from the group consisting of: hydroxyl, halo, nitro, CF_3, C1-C4 straight or branched alkyl or alkenyl, O-(C1-C4) straight or branched alkyl or alkenyl, and Ar, wherein Ar is selected from the group consisting of: 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, phenyl and phenyl having one to three substituents that are independently selected from the group consisting of: hydroxyl, halo, nitro, CF_3, C1-C4 straight or branched alkyl or alkenyl, O-(C1-C4) straight or branched alkyl or alkenyl; wherein no more than two Ar groups may be linked together;

wherein if L is an amino acid, then M is O-(C1-C4) straight or branched alkyl, O-benzyl, NH-Phenyl, or NH-4-nitrophenyl and is attached to the amino acid carbonyl;

wherein the stereochemistry at all positions being R or S, and preferably the stereochemistry is S at L if L is an α-amino acid, and at those positions marked with asterisks; however, when J is sulfhydryl, and the preferred stereochemistry of the asterisked position immediately adjacent to the nitrogen is R;

and compounds of the formula:

formula 6



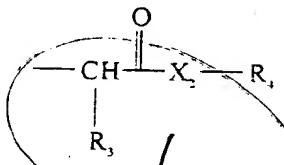
wherein, R1 is selected from the group consisting of a C1-C9 straight or branched chain alkyl or alkenyl group optionally substituted with C3-C8 cycloalkyl, C3 or C5 cycloalkyl, C5-C7 cycloalkenyl, or Ar1, where said alkyl, alkenyl, cycloalkyl or cycloalkenyl groups may be optionally substituted with C1-C4 alkyl, C1-C4 alkenyl, or hydroxy, where Ar1 is selected from the group consisting of 1-naphthyl, 2-naphthyl, 2-indolyl, 3-indolyl, 2-furyl, 3-furyl, 2-thiazolyl, 2-thienyl, 3-thienyl, 2-, 3-, 4-pyridyl, and phenyl, having one to three substituents that are independently selected from the group consisting of hydrogen, halo, hydroxyl, nitro, trifluoromethyl, C1-C6 straight or branched alkyl or alkenyl, C1-C4 alkoxy or C1-C4 alkenyloxy, phenoxy, benzyloxy, and amino;

wherein X is selected from the group consisting of oxygen, sulfur, methylene (CH_2), or H_2;

wherein Y is selected from the group consisting of oxygen or NR_2, where R_2 is hydrogen or C1-C6 alkyl; and

wherein Z is selected from the group consisting of C2-C6 straight or branched chain alkyl or alkenyl, wherein the alkyl chain is substituted in one or more positions with Ar_1 as defined above, C3-C8 cycloalkyl, cycloalkyl connected by a C1-C6 straight or unbranched alkyl or alkenyl chain and Ar_2, where Ar_2 is selected from the group consisting of 2-indolyl, 3-indolyl, 2-furyl, 3-furyl, 2-thiazolyl, 2-thienyl, 3-thienyl, 2-, 3-, or 4-pyridyl, and phenyl, having one to three substituents that are independently selected from the group consisting of hydrogen, halo, hydroxyl, nitro, trifluoromethyl, C1-C6 straight or branched alkyl or alkenyl, C1-C4 alkoxy or C1-C4 alkenyloxy, phenoxy, benzyloxy, and amino;

wherein Z may also be the fragment:



where R_3 is selected from the group consisting of straight or branched alkyl C1-C8 optionally substituted with C3-C8 cycloalkyl, or Ar_1 as defined above, and unsubstituted Ar_1;

wherein X_2 is O or NR_5, where R_5 is selected from the group consisting of hydrogen, C1-C6 straight or branched alkyl and alkenyl;

wherein R_4 is selected from the group consisting of phenyl, benzyl, C1-C5 straight or branched alkyl or alkenyl, and C1-C5 straight or branched alkyl or alkenyl substituted with phenyl;

~~wherein the stereochemistry at position 1 is R or S.~~

14. A method of identifying a FK506 analog that stimulates nerve cell growth, the method comprising:

screening FK506 analogs for binding to FKBP-12;

selecting one or more FK506 analogs of interest that bind FKBP-12 with a K_d of at least 10 μM; and

performing additional assaying of one or more of the analogs of interest for activity in promoting nerve cell growth.

15. The method of claim 14, wherein the additional assaying comprises exposing a cell to the analog of interest and determining if neurite outgrowth is promoted.

16. The method of claim 14, wherein selecting one of more FK506 analogs comprises selecting one or more analogs of interest that bind FKBP-12 with a K_d of at least 30 μM.